REMARKS

Status Summary

Claims 15-20 are pending. Claims 1-14 were canceled previously. Claims 19-20 are presently canceled. Claim 15 is amended. The applicants originally elected without traverse pending claims 15-20, directed to methods of treating an SSTR-related disorder. In response to an election of species requirement, the applicants elected the somatostatin analog of claim 18. This species was free of the prior art. The search was subsequently broadened by the examiner to include species encompassing SEQ ID NOS. 1-7, which were also found free of the prior art. A subsequent expanded search resulted in a rejection under 35 U.S.C. 103(a), which was overcome by the applicants. The search was again broadened, resulting in a rejection under 35 U.S.C. 102(b), which was also overcome by the applicants. In the present official action, the examiner maintains the rejection of claims 15-20 under 35 U.S.C. § 112, first paragraph, as allegedly lacking written description. Claim 15 is newly rejected under 35 U.S.C. 102(b) as allegedly anticipated by U.S. Patent No. 5,783,170 to Dean *et al.* ("Dean") and as evidenced by U.S. Patent No. 4,925,650 to Nosco *et al.* ("Nosco"). Reconsideration in view of the amendments and the following remarks is respectfully requested.

Finality of the Rejection

The examiner states that the new rejection under 35 U.S.C. § 102(b), as described further below, was necessitated by the applicants' amendment of claim 15 in the June 18, 2007, response to the January 16, 2007, official action, Official action, page 14. The applicants disagree with the finality of the rejection. Prior to the June 18, 2007, response, claim 15 was directed to a method for treating an SSTR-associated disorder in a mammalian subject, comprising administering to the subject (a) a composition comprising a stomatostatin analog, A-B, wherein A is a peptide chain comprising one or more cysteine residues and B is a somatostatin peptide or fragment threof, which binds to a somatostatin receptor, and (b) is a therapeutic agent, which is bound via a thiol linkage to one or more cysteine residues of A at an interior site. In the June 18, 2007, response, claim 15 was only amended for language consistency with claim 16. Specifically, claim

15 was amended to specify that A is a peptide chain *or a single amino acid* comprising one or more cysteines.

As described below, the present claims are rejected as allegedly anticipated by Dean. The examiner relies on Dean as disclosing a cysteine-containing *peptide chain*, (rather than a single amino acid), which is bound to a somatostatin peptide. According to the examiner, Tc-99m, an alleged therapeutic agent, is bound to the cysteine-containing peptide chain (referred to as 'a metal ion-complexing moiety' in Dean). The applicants submit that this new rejection is directed to the original subject matter of claim 15, which specified that a therapeutic agent is bound via a thiol linkage to the one more cysteines of A, a peptide chain, at an interior site. Based on the foregoing, the applicants submit that the new rejection under 35 U.S.C. § 102(b) was not necessitated by amendment. Accordingly, the finality of the rejection is improper and the applicants respectfully request that the finality of the rejection be withdrawn.

Rejection of Claims Under 35 U.S.C. § 112, First Paragraph, - Written Description

The examiner maintains the rejection of claims 15-20 under 35 U.S.C. § 112, first paragraph, as allegedly lacking written description. The examiner states that the specification fails to provide a representative number of species to support the genus of A-B thiol-containing conjugates, as set forth in claims 15-20, Official action, pages 6-7. In particular, the examiner contends that the genus of somatostatin peptides, and fragments thereof, as described in the instant claims, is not adequately supported by the specification, Official action, page 6. For example, the examiner asserts that the specification does not provide guidance for larger somatostatin peptides encompassing SEQ ID NOS. 1-7 or additional variants of somatostatin peptides, Official action, page 6. The examiner further asserts that the instant specification does not sufficiently exemplify the entire scope of somatostatin analogues of formula A-B, conjugated to therapeutic agents, nor is a correlation between the structure and function of the instant conjugates disclosed, Official action, page 7. The examiner also alleges that the present application inadequately demonstrates the biological activity of the instant conjugates in the treatment of SSTR-associated disorders, Official action, page 7 and pages 11-12.

In order to comply with the written description requirement, "[t]he applicant must . . . convey to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention." *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64 (Fed. Cir. 1991). The descriptive text needed to meet these requirements "varies with the nature and scope of the invention at issue, and with the scientific knowledge already in existence." *Capon v. Eshhar*, 418 F.3d 1349, 1357, 76 USPQ2d 1078, 1084 (Fed. Cir. 2005). As stated in *Capon*, the specification does not need to describe every permutation of a claimed combination to comply with the written description requirement. *Id*. at 1086

Claims 19-20 are canceled. Accordingly, the rejection is moot in regard to these claims. Independent claim 15, as amended, is directed to a method for treating an SSTR-associated cancer in a mammalian subject in need thereof, the method comprising: administering to the subject a conjugate comprising: (a) a somatostatin analog of the formula: (A – B), which comprises (i) A, which is a peptide chain or a single amino acid comprising one or more cysteine residues; and (ii) B, which is a naturally occurring or synthetic somatostatin peptide, or fragment thereof, which binds to a somatostatin receptor; and (b) a therapeutic agent, which is bound to the somatostatin analog (A – B) via a thiol linkage to the one or more cysteine residues of (A) at an interior site(s); wherein the therapeutic agent is selected from the group consisting of a radioisotope, a cytotoxin, an immunostimulatory agent, an anti-angiogenic agent, and a chemotherapeutic agent. Support for this amendment is found in pending claims 19-20, now canceled. Claim 15 is amended without prejudice and the applicants reserve the right to claim the subject matter in one or more divisional or continuation applications.

The applicants submit that a skilled artisan at the time of the invention was well-able to envision the genus of somastatin peptides and fragments thereof, as specified in the instant claims. Various classes of somatostatin analogs capable of binding to somatostatin receptors were well-known, as of the priority date of the instant application. These somatostatin analogs include amino acid-deleted or substituted naturally occurring somatostatin peptide (*i.e.*, SS-14) compounds, dicarba analogs, bicyclic octapeptide analogs, and cyclic hexapeptides (*see, e.g.* Sheridan *et al. Amer. Zool.*, "*Structure-Function Relationships of the Signaling System for the Somatostatin Peptide Hormone Family*," 2000, 40:269-286, pages 273-274, enclosed). The applicants also submit that

the instant specification adequately describes the instant genus of somatostatin peptides and fragments thereof. The present application provides *no less than 16 patents* incorporated by reference, which provide *numerous* species of somatostatin peptides that may be used in the instant methods, (*see*, page 6, lines 16-21 in the specification as originally filed for the list of patents and the information disclosure statement submitted April 5, 2004).

The 16 patents disclose naturally occurring somatostatin peptides, synthetic somatostatin peptides, and variants of such peptides. For example, U.S. Patent No. 5,750,499 describes naturally occurring somatostatin peptides (*see, e.g.* column 1, lines 13-30 of the '499 patent) and U.S. Patent No. 4,885,101 further describes variants of naturally occurring somatostatin peptides, *e.g.*, where the eighth amino acid is D-Trp, rather than the naturally occurring L-Trp (*see, e.g.*, column 1, lines 1-20 of the '101 patent). U.S. Patent No. 4,853,371 also describes somatostatin analogs containing fewer than the naturally occurring fourteen amino acids (*see, e.g.*, column 1, lines 59 to 68 and column 3, lines 1-4).

Numerous additional species of somatostatin peptides are also described in the cited patents. For example, U.S. Patent No. 6,465,613 provides at least 10 species of somatostatin peptides (*see, e.g.*, column 6, lines 12-31 of the '613 patent). At least 69 species of somatostatin peptides are described in U.S. Patent Nos. 6,001,801, 5,633,263 and 5,260,675, (*see, e.g.* columns 2 lines 24-66 and column 3, lines 1-9 of the '801 patent, column 2, lines 46-54 of the '263 patent, column 11, lines 30-59 of the '675 patent) and U.S. Patent No. 5,597,894 provides at least 6 species of multi-tyrosinated somatostatin peptides (*see, e.g.*, columns 21-22, Table 2 of the '894 patent). Additional somatostatin peptides variants are also disclosed in U.S. Patent No. 5,411,943, (*i.e.*, at least 7 species of octapeptide somatostatin analogues are disclosed at column 1, lines 63-65, and column 2, lines 1-10 in the '941 patent). In addition, the above described patents as well as U.S. Patent Nos. 5,770,687, 5,750,499, 5,708,135, 5,663,263, 5,073,541, 4,904,642, 4,871,717, 4,853,371 and 4,485,101 describe genera and subgenera of somatostatin peptides. Accordingly, contrary to the examiner's assertion, somatostatin analogs are exhaustively described in the instant specification.

Furthermore, at least U.S. Patent No. 5,597,894 describes somatostatin analogs comprising SEQ ID NO. 4 (*see e.g.* columns 3-4, compound (e) and column 30, claim 2). Accordingly, contrary to the examiner's assertion, somatostatin variants that are larger than SEQ ID NO: 4 and which encompass SEQ ID NO: 4 are described in the instant specification.

A skilled artisan at the time of the invention would also have been able to readily envision the correlation between the structure of the instant conjugates, (*i.e.*, the instant somatostatin peptides conjugated to the instant anti-cancer agents) and their function. For example, a skilled artisan recognized that the molecular heterogeneity of the somatostatin family of peptides was due to the tissue specific variation in the biosynthesis of somatostatin from larger precursor molecules (*see, e.g.* Sheridan page 273, left column). A skilled artisan also recognized that the amino acid terminus of naturally occurring somatostatin-14 (SS-14) was unlikely to be required for biological activity, *i.e.* receptor binding on target cells, (*see, e.g.* Sheridan et al. page 273, and page 274, paragraph 1), and that the size of somatostatin was unlikely to be crucial for activity (Sheridan *et al.*, page 273, right column). In addition, a skilled artisan was aware that the sequence Phe-Try-Lys-Thr is likely important to bioactivity of native somatostatin (Sheridan *et al.*, page 273, right column). Accordingly, a skilled artisan could envision the somatostatin peptide variants that would retain their somatostatin peptide binding function.

A skilled artisan would also have been able to envision the anti-cancer agents that are bound to the instant somatostatin analogs. A skilled artisan was well-aware at the time of the invention of the structure of the radioisotopes, cytotoxins, immunostimulatory agents, anti-angiogenic agents, and chemotherapeutic agents, as specified in the instant claims, and their function as anti-cancer agents. These agents are also exemplified in the instant specification on pages 18-20 in originally filed application. Methods of binding the anti-cancer agents to the somatostatin analogs are also disclosed (*see, e.g.*, page 7, lines 30-33, and page 8, lines 1-7).

The present application also adequately demonstrates that the instant conjugates may be used to treat SSTR-associated cancers. The present specification explains that the conjugates may be used to treat cancers that are associated with abnormal SSTR

expression and/or function. Such cancers are described in the instant specification and are well-known in the art (*see, e.g.*, page 3, lines 5-23, page 16, lines 12-15, page 17, lines 9-24 of the specification as originally filed). Furthermore, as stated in the previous response of June 18, 2007, the instant specification provides examples demonstrating the structure and biological activity of two species of somatostatin analog/anti-cancer agent conjugate. Examples 4 and 5 describe the cytotoxic and anti-tumor effect of CP1-AEB and CP1-FKMMAE, respectively. As stated in *Capon*, the specification does not need to describe every permutation of a claimed combination to comply with the written description requirement. Thus, based upon the specific examples provided in the specification, which are supported by the general teachings and knowledge in the art, as described above, a skilled artisan would understand the co-inventors to be in possession of the full scope of conjugates useful for performing the claimed methods. Thus, the specification provides a thorough description of the elements that may be used to derive the claimed A-B peptide thiol-containing conjugates, as well as how these elements are combined. Accordingly, a skilled artisan can readily envision the genus of instant conjugates that may be used to treat SSTR-associated cancers.

Based on the foregoing, the instant specification provides a skilled artisan with sufficient disclosure to allow him to readily envision the structure and properties of the conjugates for practice of the claimed methods. For the reasons set forth above, the applicants submit that the present specification complies with 35 U.S.C. § 112, first paragraph. Accordingly, the applicants respectfully request that the rejection of claims 15-20 be withdrawn.

Rejection of Claims Under 35 U.S.C. § 102(b)

Claims 15-20 are rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Dean as evidenced by Nosco. Based upon the following, the applicants traverse the rejection.

To anticipate a claim, the examiner must show that the cited reference teaches every element of the claim. "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art

reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). See MPEP § 2131.01.

The instant claims are directed to a method for treating an SSTR-associated disorder in a mammalian subject in need thereof, the method comprising administering to the subject a conjugate comprising:(a) a somatostatin analog of the formula: (A – B), which comprises (i) A, which is a peptide chain or a single amino acid comprising one or more cysteine residues; and (ii) B, which is a naturally occurring or synthetic somatostatin peptide, or fragment thereof, which binds to a somatostatin receptor; and (b) a therapeutic agent, which is bound to the somatostatin analog (A – B) via a thiol linkage to the one or more cysteine residues of (A) at an interior site(s); whereby a SSTR-associated disorder is treated.

Dean teaches a somatostatin analogue comprising somatostatin and a metal ion-complexing moiety, which is covalently linked to a radioimaging label, *i.e.*, Tc-99m (*see, e.g.*, column 1, lines 16-24, column 7, lines 10-15, column 11, lines 24-29). The examiner relies on Nosco to demonstrate that Tc-99m forms a thiol linkage to the cysteine in the metal ion-complexing moiety. Dean also teaches that therapeutic agents, such as a conversion electron emitting radioisotope, copper, zinc or rhenium, are "complexed" with the metal-ion complexing moiety, (*see, e.g.*, column 9, lines 4-5, lines 38-50 in Dean). Dean also teaches that the somatostatin analogues themselves may be used as therapeutic agents (*see, e.g.* column 8, lines 58-65 in Dean)

Dean does not teach all of the elements of the instant claims. Tc-99m as described in Dean is an *imaging agent*. In contrast, the instant claims specify that a *therapeutic agent* selected from a radioisotope, a cytotoxin, an immunostimulatory agent, an anti-angiogenic agent, or a chemotherapeutic agent, is bonded to the somatostatin analogue. In addition, the therapeutic agents that are disclosed in Dean are not bound to the somatostatin analog (A – B) via a thiol linkage to the one or more cysteine residues of (A) at an interior site(s), as specified in the instant claims, but are merely "complexed." The term "complexed" does not indicate a thiol linkage to a cysteine of the metal ion-complexing moiety of Dean. Accordingly, Dean fails to expressly disclose all of the features of the instant claims. Based on the foregoing, the applicants respectfully request that the rejection under 35 U.S.C. § 102(b) be withdrawn.

Conclusion

All rejections having been addressed, it is respectfully submitted that the present application is in condition for allowance and a notice to that effect is earnestly solicited. If any points remain in issue, which the examiner feels may be best resolved through a personal or telephone interview, he is kindly requested to contact the undersigned attorney at the telephone number listed below.

Respectfully submitted,

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